REMARKS/ARGUMENTS

Prior to the present amendment, Claims 58-65, 68-70, 74-77 and 86-87 were pending in this application. With this amendment, Claims 60-61 and 74 have been amended to clarify what Applicants have always regarded as their invention. The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Claims 58-65, 68-70, 74-77 and 86-87 are pending after entry of the instant amendment.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §102(a) and §102(b). The remaining rejections of the claims under 35 U.S.C. §112, first and second paragraphs, are addressed below.

I. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 61-62 and 74-77 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner asserts that Claims 61-62 and 74-77 are indefinite for reciting "the amino acid sequence of the full-length coding sequence of the nucleic acid sequence..." because an amino acid sequence and a nucleic acid sequence are chemically distinct molecules.

As amended herein, Claims 61 and 62 (and therefore, dependent Claims 74-77) recite "the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the nucleic acid sequence..."

The Examiner further asserts that Claim 74 is indefinite for the recitation of "the nucleic acid," because it is allegedly unclear if this refers to the specific nucleic acids recited in parts (a), (b), (c) or (d) of Claims 59-62 or to the "isolated nucleic acid" having the recited sequence identity to the nucleic acids of parts (a), (b), (c) or (d) of Claims 59-62.

Without acquiescing to the propriety of the rejection, and solely in order to expedite prosecution of the instant case, Claim 74 has been amended to recite "the isolated nucleic acid..." Thus it would be clear to one of ordinary skill in the art that Claim 74 refers to the "isolated nucleic acid" having the recited sequence identity to the nucleic acids of parts (a), (b), (c) or (d) of Claims 59-62.

Accordingly, the metes and bounds of the claims are clear, and withdrawal of the rejection of Claims 61-62 and 74-77 under 35 U.S.C. §112, second paragraph, is respectfully requested.

II. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62, 74-77 and 86-87 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The Examiner asserts that the specification "does not provide sufficient written description as to the structural features of the claimed genus of PRO337 nucleic acids and encoded polypeptides and the correlation between structure and function of the genus of PRO337 nucleic acids, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded." (Page 4 of the instant Office Action).

Applicants submit, for the reasons set forth below, that the specification provides an adequate written description for the claimed PRO337 nucleic acid variants.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[1,2] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[3] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [4,5]

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[1] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[2] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[3] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[4] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[5] *See also* M.P.E.P. §2163 II(A).

In *Environmental Designs, Ltd. v. Union Oil Co.*,[6] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[7] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[8,9]

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the full-length PRO337 polypeptide of SEQ ID NO:523, with or without its signal sequence. The Examiner has acknowledged that nucleic acids comprising SEQ ID NO:522 and nucleic acids encoding SEQ ID NO:523 meet the written description provision of 35 U.S.C. §112, first paragraph. (Page 8 of the instant Office Action). Thus, the genus of nucleic acids with at least 85% identity to SEQ ID NO:522, or at least 90% identity to the coding region of SEQ ID NO:522, wherein the encoded polypeptide is a mitogen for inner ear supporting cells, as well as nucleic acids that encode polypeptides with at least 95% sequence identity to SEQ ID NO:523, which possess the functional property of being a mitogen for inner ear supporting cells, would meet the requirement of 35 U.S.C. §112, first paragraph as providing adequate written description.

Applicants have provided native PRO sequence SEQ ID NO:523, and SEQ ID NO:522 which encodes it. The present application also describes methods for identifying proteins which are mitogens for inner ear supporting cells. Example 116 of the present application provides step-by-step guidelines and protocols for the proliferation of rat utricular supporting cells assay.

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[6] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[7] *See also* M.P.E.P. §2141.03.

[8] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[9] See *also* M.P.E.P. §2141.03.

By following the disclosure in the specification, one skilled in the art can easily test whether a polypeptide encoded by a variant PRO337 nucleic acid is a mitogen for inner ear supporting cells.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether an encoded variant PRO337 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Methods of isolating nucleic acid sequences encoding PRO polypeptides and polypeptide variants are described in the specification at, for example, page 185, lines 10-35; page 190, line 32, to page 191, line 8; and page 135, lines 7-21.

"An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[10] As discussed above, Applicants have recited structural features, namely, 85% sequence identity to the nucleic acid of SEQ ID NO:522, or 95% sequence identity to the polypeptide of SEQ ID NO:523, which are common to the genus. Applicants have also provided guidance as to how to make the recited nucleic acids encoding variants of SEQ ID NO:523, including listings of exemplary and preferred sequence substitutions. The genus of claimed nucleic acids is further

[10] M.P.E.P. §2163 II(A)(3)(a)

defined by having a specific functional activity for the encoded polypeptide, as a mitogen for inner ear supporting cells. Accordingly, a description of the claimed genus has been achieved.

The Examiner asserts that "[i]t has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities." (Page 5 of the instant Office Action). In support of this assertion, the Examiner cites references by Skolnick *et al.*, Burgess *et al.*, and Lazar *et al.* The Examiner concludes that "applicant's reliance on the activity of the PRO337 polypeptide encoded by SEQ ID NO:522" does not provide sufficient written description for the claimed genus of nucleic acids because allegedly "ordinary artisans could not predict the operability in the invention of any species other than the one disclosed (Page 7 of the instant Office Action).

Applicants note that Skolnick *et al.* is a review article of computational predictions of protein structure and function from sequence data. The authors are concerned with structural and functional predictions for unknown proteins, and say nothing about the effects of amino acid substitutions on the function of known proteins.

Burgess *et al.* disclose that substitution of glutamic acid for lysine results in a substantial loss of activity for the acidic fibroblast growth factor, a member of the heparin-binding growth factor family. Applicants note that the authors mutated a residue already known to be important for activity (page 2130, col. 1), and intentionally made a highly non-conservative substitution, of a negatively charged residue for a positively charged one. Lazar *et al.* disclose that in transforming growth factor alpha, the replacement of an aspartic acid residue resulted in reduction of biological activity. Again, the authors mutated a residue known to be highly conserved in the entire EGF-like family of peptides (page 1247, col. 1). Even so, of the four substitutions made, only two resulted in any loss of activity (Abstract). Thus Burgess *et al.* or Lazar *et al.* confirm that most single amino acid changes, particularly conservative changes, do not affect protein structure or function.

Further, there is no structural or functional similarity between the PRO337 polypeptide and the proteins disclosed by Burgess *et al.* and Lazar *et al.* The PRO337 polypeptide is structurally homologous to members of the IgLON subfamily of the immunoglobulin superfamily, and has activity as a mitogen of inner ear supporting cells, while the teachings of Burgess *et al.* and Lazar *et al.* are limited to the heparin-binding growth factors and the EGF-like growth factors, respectively. Thus there is no basis for extrapolating the results obtained with

these structurally and functionally completely different proteins to the predictability of the effect of mutations on the PRO337 polypeptide.

The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

As discussed above, the procedures for making the recited variant proteins are well known in the art and described in the specification. The specification also provides an assay, shown in Example 116, for detecting the recited functional activity of the variant polypeptides. Finally, the recited variant proteins encoded by the claimed nucleic acids possess both the specified functional activity and a defined degree of sequence identity to the reference sequence, SEQ ID NO:523. Accordingly, the recited variants, and the claimed nucleic acids that encode them, meet the standards set forth in the Written Description Guidelines.

Withdrawal of the written description rejection of Claims 58-62, 74-77 and 86-87 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

III. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Scope of Enablement)

Claims 58-62, 74-77 and 86-87 are rejected under 35 U.S.C. §112, first paragraph, allegedly "because the specification, while being enabling for the isolated nucleic acids comprising SEQ ID NO:522 and nucleic acids encoding the polypeptide of SEQ ID NO:523, does not reasonably provide enablement for isolated nucleic acids having at least 85% sequence identity with the nucleic acid of SEQ ID NO:522 or nucleic acids encoding a polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of SEQ ID NO:523." (Page 9 of the instant Office Action).

Applicants submit that, based upon the disclosure provided in the specification, one of ordinary skill in the art would understand how to make and use the claimed nucleic acid variants, for example in the therapeutic treatment of hearing loss, without any further experimentation.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [11,12] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[13] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[14,15]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important."[16,17] "Limitations and examples in the specification do not generally limit what is covered by the claims" M.P.E.P. § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through

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[11] M.P.E.P. §2164.01.

[12] *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

[13] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

[14] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (C.C.P.A. 1977).

[15] M.P.E.P. §2164.06.

[16] M.P.E..P. §2164.08.

[17] *In re Marzocchi*, 439 F.2d 220, 223-4, 169 USPQ 367, 370 (C.C.P.A. 1971).

illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[18]

The Disclosure provides sufficient information to enable the claimed invention

Claims 58-62 and 86-87, and consequently dependent Claims 74-77, are directed to a genus of nucleic acids having at least 85% identity to SEQ ID NO:522, or encoding polypeptides which are at least 95% identical to SEQ ID NO:523, and which have a specific and useful function (*i.e.* to a genus of nucleic acids encoding polypeptides which are mitogens for inner ear supporting cells). The claimed sequences may be used, for example, in the therapeutic treatment of hearing loss.

Applicants have provided the amino acid sequence of SEQ ID NO:523, as well as the nucleic acid sequence of SEQ ID NO:522 which encodes it. The Examiner has acknowledged that the specification is enabling for SEQ ID NO:522 which encodes SEQ ID NO:523. (Page 9 of the instant Office Action).

Example 116 of the present application provides step-by-step guidelines and protocols for the proliferation of rat utricular supporting cells assay. By following the disclosure in the specification, one skilled in the art can easily test whether a polypeptide encoded by a variant PRO337 nucleic acid is a mitogen for inner ear supporting cells.

The specification further describes methods for the determination of percent identity between two amino acid sequences (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 10, to page 183, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Accordingly, one of skill in the art could identify whether an encoded variant PRO337 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is

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[18] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward). Methods of isolating nucleic acid sequences encoding PRO polypeptides and polypeptide variants are described in the specification at, for example, page 185, lines 10-35; page 190, line 32, to page 191, line 8; and page 135, lines 7-21.

The Examiner asserts that "Applicants provide little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the PRO337 protein that are tolerant to change and the nature and extent of changes that can be made in these positions." (Page 10 of the instant Office Action). To the contrary, as discussed above, the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 9 to page 183, line 8), including a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182).

The Examiner further asserts that "there is no exemplary guidance presented in the specification to assist one skilled in the art in making and using the variants having the claimed specificity." (Page 10 of the instant Office Action). As discussed in the M.P.E.P., § 2164.08, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." Given that, as discussed above, one of ordinary skill in the art could make and use the claimed variant sequences without any undue experimentation, there is no requirement that the specification provide examples of such variant polypeptides.

The Examiner next asserts that "the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn using predicted structural determinations to ascertain binding or functional aspects and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation." (Pages 10-11 of the instant Office Action). In support of these assertions, the Examiner cites references by Bowie *et al.*, Wells *et al.*, and Ngo *et al.*

Applicants note that Ngo *et al.* is a review article of computational predictions of protein structure and function from sequence data. The authors are concerned with structural and functional

predictions for unknown proteins, and say nothing about the effects of amino acid substitutions on the function of known proteins.

Applicants further respectfully submit that the additional references do not support the Examiner's position. For example, Wells *et al.* teaches that most mutations have small effects, and "to design large changes in function will often require mutation of more than one functional residue" (page 8509, col. 1). The teachings of Bowie *et al.* confirm that "**proteins are surprisingly tolerant of amino acid substitutions**" (page 1306, col. 2; emphasis added). Thus Wells *et al.* and Bowie *et al.* confirm that most single amino acid changes, particularly conservative changes, do not affect protein structure or function.

Accordingly, one of ordinary skill in the art would be able to use the guidance provided in the specification, including the listing of conservative amino acid substitutions provided in Table 6, to make nucleic acids encoding variants of SEQ ID NO:523 that would be expected to retain the activity of SEQ ID NO:523 as a mitogen for inner ear supporting cells.

Applicants further note that the claims are not directed to all possible variants having at least 95% amino acid sequence identity to SEQ ID NO:466, but only to those variants which retain the function of the polypeptide as a mitogen for inner ear supporting cells. The specification provides the protocol for the proliferation of rat utricular supporting cells assay, as disclosed in Example 116. It would be a simple matter for one skilled in the art to test the encoded polypeptides to see if they are mitogens for inner ear supporting cells using the methods of Example 116. This would not require undue experimentation.

The claims recite nucleic acids encoding polypeptide sequences associated with a biological activity. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed nucleic acid sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be

complex does not necessarily make it undue, if the art typically engages in such experimentation."[19]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of nucleic acids having at least 85% sequence identity with the nucleic acid of SEQ ID NO:522 or nucleic acids encoding a polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of SEQ ID NO:523, wherein the polypeptide is a mitogen for inner ear supporting cells, can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

Accordingly, withdrawal of the enablement rejection of Claims 58-62, 74-77 and 86-87 under 35 U.S.C. §112, first paragraph, is respectfully requested.

[19] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C66**).

Respectfully submitted,

Date: October 5, 2005

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